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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,716	10/18/2004	Yoshihiro Hakamada	260068US0PCT	2844

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	**PAPER NUMBER**
1652	

NOTIFICATION DATE	DELIVERY MODE
08/15/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/510,716	HAKAMADA ET AL.	
	Examiner	Art Unit	
	Ganapathirama Raghu	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-8,10,11,14,17 and 19-22* is/are rejected.

7)☒ Claim(s) *2, 3, 5, 12, 13, 15, 16 and 18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/29/07 has been entered.

In response to the Final Office Action mailed on 01/18/2007 and further an Advisory Action mailed on 05/10/2007, applicants' filed an RCE received on 06/18/07 is acknowledged. Thus, claims 1-8, and 10-22 are pending in the instant Office Action and are now under consideration.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). This application is a 371 of PCT/JP03/05371 filed on 04/25/2003 and claims the priority date of Japanese application 2002-124474 filed on 04/25/2002. However, examiner notes that the English translation for the Japanese application 2002-124474 has not been provided.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 18 Oct. 2004 and 09 Aug. 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, examiner is considering the information disclosure statement.

Drawings

The drawings are considered for examination purposes only.

Objections-Abstract

Abstract of the disclosure is objected to because abstract should be on a separate sheet of paper, Correction is required. See MPEP § 608.01(b).

Maintained- Claim Rejections: 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claim 1 and claims 4, 6-8, 10-11, 14, 17 and 19-22 depending therefrom are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an alkaline cellulase which is obtained by deleting a peptide consisting of one or more residues chosen from the 357th to 362nd positions of SEQ ID NO: 2 or from the corresponding positions of SEQ ID NOs: 7, 8 and 9 or an alkaline cellulase having at least 95% sequence identity to SEQ ID NO: 2 and replacing the peptide with an insertion peptide having 2-5 amino acid residues, expression vector and isolated host cell comprising said polynucleotides, does not reasonably provide enablement for any alkaline cellulase from any source which is obtained by deleting a peptide consisting of one or more residues chosen from 343rd to 377th positions of SEQ ID NO: 2 or from corresponding positions of SEQ ID NOs: 7, 8 and 9 or an alkaline cellulase having at least 95% sequence identity to SEQ ID NO: 2 and replacing the peptide with an insertion peptide having 2-15 amino acid residues, to a gene encoding said mutated polypeptide, vector and an

isolated host cell comprising said polynucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 4, 6-8, 10-11, 14, 17 and 19-22 are so broad as to encompass any alkaline cellulase from any source which is obtained by deleting a peptide consisting of one or more residues chosen from 343rd to 377th positions of SEQ ID NO: 2 or from corresponding positions of SEQ ID NOs: 7, 8 and 9 or an alkaline cellulase having at least 95% sequence identity to SEQ ID NO: 2 and replacing the peptide with an insertion peptide having 2-15 amino acid residues. The scope and the breadth of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded

proteins' structure relates to its function. However, in this case the disclosure is limited to an alkaline cellulase which is obtained by deleting a peptide consisting of one or more residues chosen from the 357th to 362nd positions of SEQ ID NO: 2 and replacing the peptide with an insertion peptide having the sequence Ala-Gly-Ala, Ala-His-Ala or Ala-Arg-Ala. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides and encoding polynucleotides. The specification is limited to teaching the use of an alkaline cellulase which is obtained by deleting a peptide consisting of residues chosen from the 357th to 362nd positions of SEQ ID NO: 2 and replacing the peptide with an insertion peptide having the sequences Ala-Gly-Ala, Ala-His-Ala or Ala-Arg-Ala, expression vector and isolated host cell comprising said polynucleotides, but provides no guidance with regard to the making of other variants and mutants from any source or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such

modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope and breadth of the claims which encompass any alkaline cellulase from any source which is obtained by deleting a peptide consisting of one or more residues chosen from 343rd to 377th positions of SEQ ID NO: 2 or from corresponding positions of SEQ ID NOs: 7, 8 and 9 or an alkaline cellulase having at least 95% sequence identity to SEQ ID NO: 2 and replacing the peptide with an insertion peptide having 2-15 amino acid residues, as in claims 1, 4, 6-8, 10-11, 14, 17 and 19-22, because the specification does not establish: (A) Which of all or a portion of a 35 residue long fragment (from positions 343rd to 377th) can be replaced except for residues 357-362 with 2-15 unspecified amino acids in the protein/polynucleotide structure without affecting the activity of the encoded cellulase; (B) the general tolerance of the polypeptide and the polynucleotide encoding cellulase to said modification and extent of such tolerance; (C) a rational and predictable scheme for said modification with any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope and breadth of the claims broadly including polypeptides with an enormous number of modifications. The scope and breadth of the claims must bear a reasonable correlation with the

scope and breadth of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). There is no guidance beyond the three specific mutants described in the specification as the breadth of the modification encompasses any amino acid residue and there is no limitation either to the deletion or introduction of peptides similar in size and properties to those of mutants disclosed. For example, applicants' have not shown or given guidance by way of any other mutant, wherein any amino acid residue with bulky aromatic group or side chain or helix breaking amino acid residue like proline has been inserted and the structure-function correlation of such a mutant. Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claim 1 and claims 4, 6-8, 10-11, 14, 17 and 19-22 depending therefrom are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4, 6-8, 10-11, 14, 17 and 19-22 are directed to any alkaline cellulase from any source which is obtained by deleting a peptide consisting of one or more residues chosen from 343rd to 377th positions of SEQ ID NO: 2 or from corresponding positions of SEQ ID NOs: 7, 8 and 9 or an alkaline cellulase having at least 95% sequence identity to SEQ ID NO: 2 and replacing the peptide with an insertion peptide having 2-15 amino acid residues, to a gene

encoding said mutated polypeptide, vector and an isolated host cell comprising said polynucleotides.

Claims 1, 6-8, 10-11, 14 and 19-22 are rejected under this section 35 U.S.C. 112, because the claims are directed to a genus of polypeptides, i.e., any alkaline cellulase from any source which is obtained by deleting a peptide consisting of one or more residues chosen from 343rd to 377th positions of SEQ ID NO: 2 or from corresponding positions of SEQ ID NOs: 7, 8 and 9 or an alkaline cellulase having at least 95% sequence identity to SEQ ID NO: 2 and replacing the peptide with an insertion peptide having the sequences Ala-Gly-Ala, Ala-His-Ala or Ala-Arg-Ala, with no support in the specification for the structural details of all the species encompassed in the genus associated with the function i.e., alkaline cellulase activity, vector and host cell has been provided in the specification for the claims. The specification discloses the isolation of an alkaline cellulase which is obtained by deleting a peptide consisting of residues chosen from the 357 to 362 positions of SEQ ID NO: 2 and replacing the peptide with an insertion peptide having 2-5 amino acid residues, expression vector and isolated host cell comprising said polynucleotides, the disclosed species which replaces a short peptide region with three specific other short peptides i.e., alanine-glycine-alanine or alanine-histidine-alanine or alanine-arginine-alanine would not be representative of scope of modification encompassed in claim 1, such that claim 1 includes alkaline cellulases obtained by deleting, from a cellulase having the amino acid sequence represented by SEQ ID NO: 2 or a homologous amino acid sequence an amino acid sequence exhibiting at least 95% homology to SEQ ID NO: 2, a peptide consisting of one or more amino acid residues chosen from positions 343-377 of SEQ ID NO: 2 or from corresponding positions of said homologous amino acid sequence and replacing the peptide with

an insertion peptide having 2-15 amino acids into at least one deleted position and having alkaline cellulase activity. No information, beyond the characterization of the polypeptide, an alkaline cellulase which is obtained by deleting a peptide consisting of one or more residues chosen from the 357 to 362 positions of SEQ ID NO: 2 and replacing the peptide with an insertion peptide having the sequences Ala-Gly-Ala, Ala-His-Ala or Ala-Arg-Ala, expression vector and isolated host cell comprising said polynucleotides, has been provided by the applicants, which would indicate that they had possession of a mutated alkaline cellulase obtained by deleting from a cellulase having the amino acid sequence represented by SEQ ID NO: 2 or a homologous amino acid sequence exhibiting at least 95% homology to SEQ ID NO: 2, a peptide consisting of one or more amino acid residues chosen from positions 343-377 of SEQ ID NO: 2 or from corresponding positions of said homologous amino acid sequence and replacing the peptide with an insertion peptide having 2-15 amino acids into at least one deleted position and having alkaline cellulase activity. The specification does not contain any disclosure of the sequence and structure of all the polypeptides within the scope of the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed. It is well known in the art that structure correlates with function and furthermore any amino acid residue or any number of amino acid residue substitutions may not be tolerated, as such substitutions may not yield a structure correlated with the desired functional activity of the molecule. The disclosed information is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus of polypeptides. Clearly the recited genera include many

proteins with very different structures with no support in the specification with the correlated functional activity of the molecule as claimed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants' have traversed both the written description and enablement rejections with the same arguments and point out that claims have been duly amended to recite that the defined sequences to be at least 95% homology to SEQ ID NO: 2 and have referred to written description guidelines of MPEP and to a reversal of BPAI case (*Ex parte Bandman*) in support of their written description and enablement traversal arguments.

Applicants' arguments have been considered and found to be non-persuasive as disclosed species is not representative of the structure of all the species encompassed in the genus and specification does not contain any disclosure of the sequence and structure of all the polypeptides within the scope of the claimed genus for the reasons cited below. Pages 8-9 of specification, wherein it is stated "Three-dimensional structural analysis through homology modeling (Ozawa et al., Protein Eng., 14, 501-504, 2001) suggests that the amino acid region at the 343rd to 377th positions of SEQ ID NO: 2 is suggested to be region that forms the loop structure that is intimately involved in **maintaining the cellulase structure**". It is well known in the art that structure correlates with function and furthermore any amino acid residue or any number of amino acid residue substitutions may not be tolerated, as such substitutions may not yield a structure correlated with the desired functional activity of the molecule. There is no guidance beyond the three specific mutants described in the specification as the breadth of the

modification encompasses any amino acid residue and there is no limitation either to the deletion or introduction of peptides similar in size and properties to those of mutants disclosed. For example, applicants' have not shown or given guidance by way of any other mutant, wherein any amino acid residue with bulky aromatic group or side chain or helix breaking amino acid residue like proline has been inserted and the structure-function correlation of such a mutant.

The disclosed information is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus of polypeptides. Clearly the recited genera include many proteins with very different structures with no support in the specification with the correlated functional activity of the molecule as claimed.

Similarly applicants' arguments for enablement rejections have been considered and found to be non-persuasive for the same reasons in countering the applicants' arguments for written description. Although applicants have shown how to make the variants by way of three examples (SEQ ID NOs: 7-9), applicants have not established how to use other claimed variants as encompassed by the claims, i.e., the structure-function correlation is not established in the specification for all the variants and mutants. While methods to produce variants of a known sequence, such as insertion mutagenesis, site-specific mutagenesis, random mutagenesis, etc., are well known to the skilled artisan, producing variants useful as claimed; any mutated alkaline cellulase obtained by deleting from a cellulase having the amino acid sequence represented by SEQ ID NO: 2 or a homologous amino acid sequence an amino acid sequence exhibiting at least 95% homology to SEQ ID NO: 2, a peptide consisting of one or more amino acid residues chosen from positions 343rd to 377th of SEQ ID NO: 2 or from corresponding positions of said homologous amino acid sequence and replacing the peptide with an insertion peptide having 2-

15 amino acids into at least one deleted position and having alkaline cellulase activity or a enzyme homologous thereto, to a gene encoding said mutated polypeptide, vector and an isolated host cell and claim 14 directed to a mutated alkaline comprising the sequence of SEQ ID NO: 7 or 8 or 9 a peptide consisting of one or more amino acid residues chosen from the positions corresponding to the 343rd to 377th positions of SEQ ID NO: 2 and replacing the peptide with an insertion peptide having 2-15 amino acid residues, requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance, one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims, this would clearly constitute **undue** experimentation.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1) Claims 1, 4, 6-8, 10-11, 14, 17 and 19-22 are rejected under 35 U.S.C. first paragraph for enablement and written description.

2) Claims 2, 3, 5, 12, 13 and 15, 16 and 18, are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Allowable Subject Matter/Conclusion

None of the claims are allowable. Claims 1-8 and 10-22 are rejected/objected for the reasons identified in the Summary section of this Office Action. Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on M-F; 8:00-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.
Patent Examiner
Art Unit 1652
July 24, 2007.

/Rebecca Prouty/
Primary Examiner
Art Unit 1652